# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 209803Orig1s000
# 209805Orig1s000
# 209806Orig1s000

# SUMMARY REVIEW

# Cross-Discipline Team Leader Review

| | |
|---|---|
| **Date** | (see electronic signature) |
| **From** | William H. Chong |
| **Subject** | Cross-Discipline Team Leader Review |
| **NDA/BLA # Supplement#** | NDA 209803<br>NDA 209805<br>NDA 209806 |
| **Applicant** | Merck Sharp and Dohme Corp |
| **Date of Submission** | December 19, 2016 |
| **PDUFA Goal Date** | December 19, 2017 |
| **Proprietary Name / Non-Proprietary Name** | STEGLATRO (ertugliflozin)<br>STEGLUJAN (ertugliflozin and sitagliptin)<br>SEGLUROMET (ertugliflozin and metformin hydrochloride) |
| **Dosage form(s) / Strength(s)** | **NDA 209803:** Once daily oral tablet (5 mg and 15 mg)<br>**NDA 209805:** Once daily oral tablet (b) (4) 5 mg/100 mg, 15 mg/100 mg [ertugliflozin/sitagliptin])<br>**NDA 209806:** Twice daily oral tablet (2.5 mg/500 mg, 2.5 mg/1000 mg, 7.5 mg/500 mg, 7.5 mg/1000 mg [ertugliflozin/metformin hydrochloride]) |
| **Applicant Proposed Indication(s)/Population(s)** | **NDA 209803:** adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus<br>**NDA 209805:** adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate<br>**NDA 209806:** adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4) |
| **Recommendation on Regulatory Action** | ***NDA 209803****: Approval*<br>***NDA 209805****: Approval*<br>***NDA 209806****: Approval* |
| **Recommended Indication(s)/Population(s)** (if applicable) | ***NDA 209803:*** *adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus*<br>***NDA 209805:*** *adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate*<br>***NDA 209806:*** *adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus* (b) (4) |

**Review Team:**

***NDA 209803 (ertugliflozin):***

| | |
|---|---|
| **Drug Substance Reviewer** | Erika Englund |
| **Drug Product Reviewer** | Elise Luong |
| **Microbiology/Process Reviewer** | Chaoying Ma |
| **Biopharmaceutics Reviewer** | Hansong Chen |
| **Facilities Reviewer** | Allison Aldridge |
| **Quality Technical Lead** | Suong Tran |
| **Pharmacology/Toxicology Reviewer** | Jessica Hawes |
| **QT-IRT** | Moh Jee Ng |
| **Clinical Pharmacology Reviewers** | Suryanarayana Sista and Lian Ma |
| **Efficacy Statistics Reviewer** | Alexander Cambon |
| **Safety Statistics Reviewer** | Elande Baro |
| **Clinical Reviewer** | Frank Pucino |
| **Office of Scientific Investigations** | Cynthia Kleppinger |
| **DPMH Reviewer** | Carrie Ceresa |
| **OPDP Reviewer** | Meena Ramachandra |
| **DMPP Reviewer** | Sharon Williams |
| **DRISK Reviewer** | Naomi Redd |
| **Project Manager** | Elizabeth Godwin |

***NDA 209805 (ertugliflozin and sitagliptin):***

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|---|---|
| **Drug Substance Reviewer** | Erika Englund |
| **Drug Product Reviewer** | Ravindra Kasliwal |
| **Microbiology/Process Reviewer** | Haui Chang |
| **Biopharmaceutics Reviewer** | Peng Duan |
| **Facilities Reviewer** | Krishna Ghosh |
| **Environmental Assessment Reviewer** | James Laurenson |
| **Quality Technical Lead** | Suong Tran |
| **Pharmacology/Toxicology Reviewer** | Jessica Hawes |
| **Clinical Pharmacology Reviewer** | Lei He |
| **Efficacy Statistics Reviewer** | Alexander Cambon |
| **Safety Statistics Reviewer** | Eland Baro |
| **Clinical Reviewer** | Frank Pucino |
| **Office of Scientific Investigations** | Cynthia Kleppinger |
| **DPMH Reviewer** | Carrie Ceresa |
| **OPDP Reviewer** | Meena Ramachandra |
| **DMPP Reviewer** | Sharon Williams |
| **DRISK Reviewer** | Naomi Redd |
| **Project Manager** | Elizabeth Godwin |

***NDA 209806 (ertugliflozin and metformin):***

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|---|---|
| **Drug Substance Reviewer** | Erika Englund |
| **Drug Product Reviewer** | Elise Luong |
| **Microbiology/Process Reviewer** | Hong Yang |
| **Biopharmaceutics Reviewer** | Kalpana Paudel |
| **Facilities Reviewer** | Michael Klapal |
| **Quality Technical Lead** | Suong Tran |
| **Pharmacology/Toxicology Reviewer** | Jessica Hawes |
| **Clinical Pharmacology Reviewers** | Lei He and Lian Ma |
| **Efficacy Statistics Reviewer** | Alexander Cambon |
| **Clinical Reviewer** | Frank Pucino |
| **Office of Scientific Investigations** | Cynthia Kleppinger |
| **DPMH Reviewer** | Carrie Ceresa |
| **OPDP Reviewer** | Meena Ramachandra |
| **DMPP Reviewer** | Sharon Williams |
| **DRISK Reviewer** | Naomi Redd |
| **Project Manager** | Elizabeth Godwin |

# 1. Benefit-Risk Assessment

**Benefit-Risk Summary and Assessment**

Type 2 diabetes mellitus (T2DM) is a condition of chronic impaired glucose homeostasis that leads to chronic hypergl
risk for vascular complications (both microvascular and macrovascular). Therapies for T2DM have focused on impro
assessed by change in hemoglobin A1c (HbA1c). While there are multiple drug products approved both as individual
combination drug products (FCDP), many patients are unable to achieve glucose targets. While reasons for this are lil
argument that has been made is that there are an insufficient number of available therapies to adequately allow for ind

In these New Drug Applications (NDAs), Merck Sharp and Dohme (hereafter referred to as the applicant) is proposing
antidiabetic drug products: ertugliflozin (a sodium glucose cotransporter-2 [SGLT2] inhibitor), ertugliflozin + sitaglip
SGLT2 inhibitor and a dipeptidyl peptidase-4 [DPP4] inhibitor), and ertugliflozin + immediate-release metformin (a c
inhibitor and a biguanide). To support these three NDAs, the applicant has conducted seven phase 3 studies to demon
lowering effect of ertugliflozin. From these studies, it can be concluded that ertugliflozin is better than placebo for im
(as assessed using hemoglobin A1c [HbA1c]). This in turn should result in improved clinical outcomes (i.e., reduced
complications) for patients with T2DM. The fixed combination drug products (FCDPs) have similarly demonstrated t
glycemic control with each of the components showing a contribution to the glycemic lowering effect.

Safety concerns for ertugliflozin include genital infections, urinary tract infections, hypoglycemia, volume depletion/h
acute kidney injury, increases in hematocrit, increases in LDL-C, and lower limb amputations. Aside from lower limb
concerns are consistent with other members of the SGLT2 inhibitor class. One member of the SGLT2 inhibitor class
limb amputations as a risk in the prescribing information and includes a Boxed Warning. The basis for that comes fro
based on a larger database than is currently available for ertugliflozin. Though there are a limited number of events to
ertugliflozin database, the signal of an increased risk for lower limb amputations that was seen is concerning. This po
communicated though I do not believe that the current data are sufficient to warrant a Boxed Warning for ertugliflozin
ongoing cardiovascular outcomes trial (CVOT) will inform whether further labeling would be appropriate in the future

The assessment of cardiovascular safety was performed using a meta-analysis of clinical trial and included interim dat
cardiovascular outcomes trial (CVOT). Based on this assessment, excess cardiovascular risk as discussed in the 2008
Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes" has bee

The safety profile of the FCDPs reflects the combined safety profiles of the components, and no clear potentiation of i

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